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ENVIRONMENTAL CARCINOGENESIS

Lifestyle Factors, Exposures, Genetic Susceptibility, and Renal Cell Cancer Risk: A Review

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Malignant kidney tumors account for approximately 2% of all new primary cancer cases diagnosed in the United States, with an estimated 30,000 cases occurring annually. Although a variety of agents, chemical and biological, have been implicated as causal agents in the development of renal cell carcinoma (RCC), the etiology remains enigmatic. The strongest association has been developed between cigarette smoking and renal cancer however consistent, positive associations between RCC and obesity, diabetes, and hypertension have also been reported. In addition, more recent investigations of familial kidney cancer syndromes indicate that a strong genetic component contributes to RCC development. Several genes have been identified through investigation of familial kidney cancer syndromes. This review article describes recent trends in RCC incidence and the currently identifiable etiological causes that account for approximately half of the RCC cases diagnoses. The remainder of this review then focuses on additional risk factors that have thus far not been well examined but may be helpful in explaining the increasing incidence trends and the geographic or racial variation observed nationally and worldwide.

Keywords Kidney cancer; Exposures; Genetic susceptibility; Review

INTRODUCTION

Malignant tumors of the kidney account for approximately 2% of all new primary cancer cases diagnosed in the United States, with an estimated 30,000 cases occurring annually.[1,2] Renal cell carcinoma (RCC) of the renal parenchyma accounts for >80% of all renal cancers, the majority of which are adenocarcinomas.[3] RCC is subdivided into several histologic subtypes. The largest group, clear cell carcinoma, accounts for 80–85% of cases followed by papillary carcinoma, accounting for about 10%. The remaining types, such as oncocytomas and chromophobe tumors, are more rare. Other less common histological types include transitional cell malignancies, most often occurring in the renal pelvis; nephroblastoma or Wilms' tumor, an embryonal malignancy of early childhood; and a mixture of sarcomas.[3]

Although a variety of agents, chemical and biological, have been implicated as causal agents in the development of RCC, the etiology, nonetheless, remains enigmatic. The strongest association has been developed between cigarette smoking and renal cancer, for both cancers of the renal parenchyma (usually referred to as renal cell) and those of the renal pelvis and ureter.[4,5] Consistent, positive associations between RCC and obesity (high relative weight), diabetes, and hypertension have also been reported.[6,7] Other risk factors associated with renal cancer include abuse of analgesics,[4,8] history of cystic disease due to long-term hemodialysis,[9] and certain occupations.[10,11]

In addition, more recent investigations of familial kidney cancer syndromes indicate that a strong genetic component contributes to RCC development.[12,13] Several genes have been identified through investigation of familial kidney cancer syndromes. The relationship between the von Hippel-Lindau (VHL) tumor suppressor gene and clear cell carcinoma,[12] the MET proto-oncogene gene and papillary carcinoma,[13] and other genes associated with inherited syndromes, such as familial oncocytoma[14] and the Birt-Hogg-Dubé syndrome[15] have provided new insights into the causal mechanism of each disease and may also be important in understanding sporadic forms of the disease.

In combination with the enigmatic nature of RCC etiology, several factors lead to a high potential for substantial cancer-related health disparities, including the relatively high occurrence of RCC among certain minorities, the large racial and geographic variations in disease incidence, the underlying genetic susceptibilities, and the continued high proportion of cases diagnosed at advanced stage, a factor related to low survival. This review article briefly describes recent trends in

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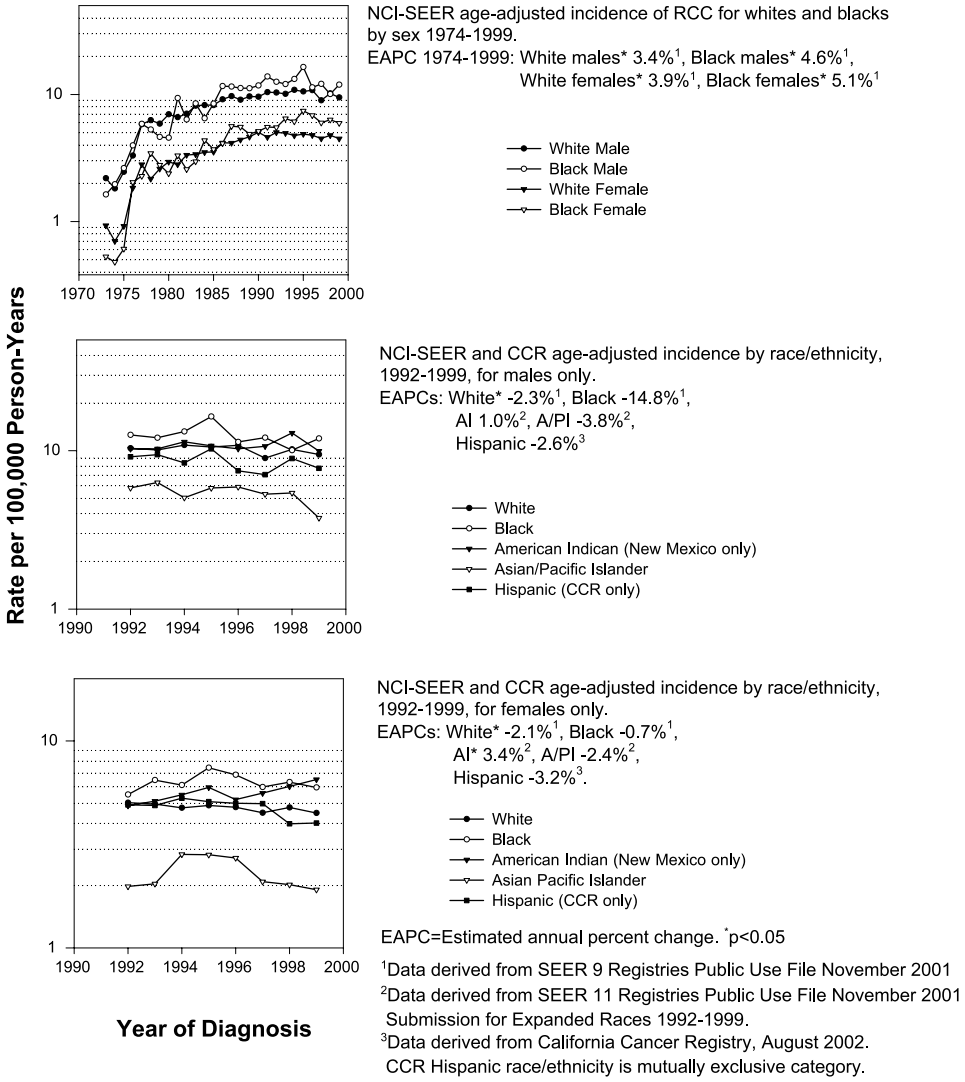

FIG. 1. Age-adjusted (2000 U.S. Standard) incidence rates for renal cell carcinoma per 100,000 person-years by sex and race/ethnicity in the United States—NCI-SEER, 1974–1999 and CCR, 1992–1999.

RCC incidence and the currently identifiable etiological causes that account for approximately half of the RCC case diagnoses. The remainder of this review then focuses on additional risk factors that have thus far not been well examined but may be helpful in explaining the increasing incidence trends and the geographic or racial variation observed nationally and worldwide.

INCIDENCE, TRENDS, AND RACIAL VARIATION

Recent descriptive studies have reported increases in the overall incidence of kidney cancer since the early 1970s, not only in the United States but also globally including portions of Asia, Oceania, Europe, and South America.[16–18] Furthermore, in the United States, increases in incidence among blacks of both sexes have outpaced increases among whites (Figure 1, top graph).[19] Most recent data (1992–1999) from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program suggest a leveling off or decrease in this trend for most racial/ethnic groups, with the exception of American Indians in New Mexico (Figure 1, bottom two graphs).[19,20] Other analyses in the United States have suggested a continued increase among Hispanic women in recent years.[21] Small numbers of cases during this short time period may or may not indicate a broader trend.

Globally, there is an eightfold variation in kidney cancer incidence.[17] Racial/ethnic differences within the United States are also significant. According to SEER data, the highest incidence occurs among American Indians in New Mexico (12.3 per 100,000), and the lowest incidence occurs among Asian/Pacific Islanders in California (2.9 per 100,000)

TABLE 1
Incident cases and age-adjusted rates for renal cell carcinoma by race/ethnic group and sex, NCI-SEER program and California, 1995–1999

	Total			Male			Female		
	Cases	AAIR	95% CI	Cases	AAIR	95% CI	Cases	AAIR	95% CI
Whites (11 SEER Registries)[a]	9071	6.6	6.5–6.8	5719	9.4	9.1–9.6	3352	4.4	4.3–4.6
Non-Hispanic Whites (California)[c]	6085	6.3	6.1–6.4	3922	9.0	8.7–9.3	2163	4.1	3.9–4.3
Blacks (11 SEER Registries)[a]	1181	8.2	7.8–8.7	713	11.5	10.7–12.5	468	5.8	5.2–6.3
Non-Hispanic Blacks (California)[c]	632	7.7	7.1–8.4	409	11.6	10.4–12.8	223	4.8	4.2–5.5
Hispanics (11 SEER Registries)[b]	1009	5.9	5.5–6.3	596	7.9	7.2–8.6	413	4.3	3.9–4.8
New Mexico SEER only[b]	241	10.0	8.7–11.4	140	12.2	10.2–14.6	101	8.0	6.5–9.7
Hispanics (California)[c]	1445	6.2	5.9–6.5	868	8.2	7.6–8.8	577	4.6	4.2–5.0
American Indians (11 SEER Registries)[a]	75	6.5	5.1–8.3	52	10.2	7.5–13.7	23	3.6	2.3–5.5
New Mexico SEER only[a]	52	12.3	9.1–16.4	34	18.7	12.8–27.3	18	7.4	4.3–12.1
Asian/Pacific Islanders (11 SEER Registries)[a]	569	3.6	3.3–3.9	370	5.2	4.7–5.8	199	2.3	2.0–2.6
Asian/Pacific Islanders (California)[c]	407	2.9	2.7–3.3	274	4.4	3.9–5.0	133	1.8	1.5–2.1

AAIR, average annual age-adjusted incidence rate per 100,000 using the 2000 U.S. Standard with 95% confidence intervals (95% CI).

[a]Data derived from SEER 11 Registries Public Use File November 2001 Submission for Expanded Races 1992–1999 includes 3 of 10 California regional registries.

[b]Data derived from SEER 11 Registries Public Use File November 2001 Submission for Hispanics 1992–1999 includes 3 of 10 California regional registries.

[c]Data derived from California Cancer Registry for cases reported as of August 2002.

(Table 1). Relative to the general U.S. population, higher rates have also been noted among American Indian and Alaska Native populations in other geographic areas.[22–25] Compared with non-Hispanic whites, Hispanics in New Mexico and black populations also have elevated renal cell cancer rates (Table 1). Racial misclassification, as well as differences in methodology used by cancer registries to determine race/ethnicity, account for some portion of the differences by registry for the same racial/ethnic group shown in Table 1.[22,23]

The underlying reasons for both the upward trends and the racial/ethnic disparity in RCC incidence remain in doubt. Although part of this increase may be attributed to inadvertent clinical detection due to the increased use of ultrasonography, computed tomography, and magnetic resonance imaging, the increasing incidence of distant and unstaged cases of RCC suggest that this increase is not solely due to earlier detection.[16]

KNOWN RISK FACTORS

Several case-control studies have been conducted to date that examined associations between lifestyle and environmental factors and renal cancer (Table 2). These studies identified a number of risk factors, most notably cigarette smoking, obesity, and hypertension. Smoking and body mass index (BMI) have demonstrated the most consistent associations with kidney cancer. The strongest association between an exposure and cancers of both the renal parenchyma and pelvis has been with cigarette smoking.[4,5,26–28] Most case-control and cohort studies have reported significant associations with cigarette smoking, with relative risks ranging from 30% to twofold, and significant dose-response trends.[5,27] The absence of significant association in a few studies may be partly explained by small sample size and the use of hospital controls with a high prevalence of smoking.[29–34] Population-based attributable risks for cigarette smoking have ranged from 27% to 37% of RCCs in men and from 10% to 24% in women.[5,35,36] Consistent positive associations between RCC and obesity have been reported among both men and women.[6,7,37] The risks tend to rise with increasing BMI. Risks for obese persons have ranged from 20% to nearly threefold, with risks generally higher for women than men.[37] Assuming a causal association, attributable risks estimated from a population-based case-control study conducted in Minnesota determined that approximately 20% of RCC cases are attributable to excess weight.[36] Obesity may contribute to risk by increasing levels of endogenous estrogens[38–40] and availability of insulin-like growth factors.[41,42] Obesity is also related to hypertension and arterionephrosclerosis, factors that

TABLE 2
Population-based case-control studies of renal cell cancer

Setting/dates of diagnosis	Study/studies	Cases/controls‡	Exposures analyzed or controlled for
Australia: New South Wales 1977–1982	[28]	360/985	S, UC, AG, AHY, diet, C, milk, EDU, SES
Australia: New South Wales 1989–1990	[5,10,53]	489/523	S, BMI, HYPT, UC, MC, AHY, DU, DP, OC, HRT, MAR, EDU, OCCU, SROC
Canada: Montreal 1979–1985	[81]	142/533	S, BMI, INC, OCCU, JEM
Canada: 8 provinces 1994–1997	[86]	1279/5370	S, BMI, A, diet, INC, EDU, SES, OCCU, SROC
Canada: Ontario 1986–1987	[4]	518/1381	S, BMI, HBP, DIAB, UC, DU, AG, FH, OC, RH, HRT, C, T, A, diet, ETHN
China: Shanghai 1987–1989	[69]	154/157	S, BMI, HYPT, DU, AG, OC, HRT, RH, diet, EDU, OCCU
Denmark 1989–1992	[6,11,57,222]	365/396	S, TOB, BMI, FH, C, T, A, diet, EDU, SES
Finland 1977–1978	[87]	338/338	S, BMI, C, OCCU, JEM
Germany: West Berlin, Bremen, Leverkusen, Halle, and Jena 1991–1995	[88]	935/4298	S, BMI, SES, OCCU, JEM
Germany: Rhein-Neckar-Edenwald 1989–1991	[94]	277/286	S, SES, MAR, urban, OCCU, SROC
International Renal Cell Cancer Study↕ 1989–1991	**	1732/2309	S, TOB, BMI, HT, WT, PA, HYPT, DIAB, UC, FH, MC, AHY, DU, AG, DP, RH, HYST, OC, HRT, A, diet, EDU, OCCU, SROC
Sweden 1996–1998	[223]	648/900	S, BMI, HYPT, DIAB, HT, BWT, EDU
Sweden 1989–1991	[224]	379/353	S, BMI, HT, WT, WT change, DP, PA
USA: Minneapolis-St. Paul, Minnesota 1974–1979	[35,90]	495/691	S, BMI, UC, AG, C, T, A, diet, ETHN, OCCU
USA: Minnesota 1988–1990	[64,117]	438/687	S, BMI, HYPT, DU, AHY, OCCU, JEM
USA: Boston Metro Area 1981–1984	[77]	518/518	S, BMI, drugs, VIT, PA, MC, diet, ETHN, OCCU
USA: Boston Metro Area 1976–1983	[68]	203/605	S, BMI, HYPT, AG, UC, MC, diet, ETHN, EDU, INC
USA: Iowa 1986–1989	[225–227]	406/2429	S, BMI, HYPT, BI, FH, PA, C, T, A, diet, OCCU
USA: Los Angeles County/1975–1979	[7]	160/160	S, BMI, HYPT, UC, DP, DU, C, T, A, HRT, RH, MAR, REL, EDU, OCCU, SROC
USA: Los Angeles County 1986–1994	[228–231]	1204/1204	S, BMI, HYPT, FH, AG, DIAB, MC, DP, DU, AHY, HYST, A, diet, EDU, OCCU
USA: Western Washington State 1996–1997	[217]	130/505	S, BMI, HBP, GST

A, alcohol; AG, analgesics; AHY, antihypertensive drugs; BMI, body mass index; BWT, birth weight; C, coffee; DIAB, diabetes; DP, diet pills; DU, diuretics; EDU, education; ETHN, ethnicity; FH, family history of kidney cancer ; GST, glutathione S-transferase polymorphisms; HBP, high blood pressure; HRT, hormone replacement therapy; HT, height; HYPT, hypertension; HYST, hysterectomy; INC, income; JEM, job exposure matrix; MAR, marital status; MC, medical conditions; OCCU, occupation; PA, physical activity; REL, religion; RH, reproductive history; SES, socioeconomic status; SROC, self-reported occupational compounds; T, tea; TOB, tobacco; UC, urologic conditions; VIT, vitamins; WT, weight.

‡Number of cases and controls may differ by analyses.

**=Refs. [27,49,70,79,94,232–234] ↕6 centers in 5 countries: Australia (Sydney), Denmark (Denmark), Germany (Berlin and Heidelberg), Sweden (Uppsala), and USA (Minnesota).

could alter the renal cell environment, making it favorable to tumor induction.[43,44] Although obesity is a stronger and more consistent risk factor in women than men, it has been suggested that female sex horemones may reduce RCC risk. A history of oophorectomy/hysterectomy is associated with an increased risk of renal cell cancer.[45–47] Similary, testosterone treatment and/or oophrectomy increase the incidence of RCC, whereas estradiol or estriol treatment and/or castration decrease the incidence of RCC in rats treated with the renal carcinogen ferric nitrilotriacetate (Fe-NTA).[48]

Hypertension has been associated with RCC in most studies, with excess risks ranging from 20% to threefold.[49–52] It remains unclear whether hypertension or treatment of hypertension is the main risk factor. Some studies have found that risks remain elevated after adjustment for antihypertensive medications,[50,53–56] others have found that risks dropped to insignificant levels,[4,7,49,57] and others have not adjusted for medications because their use is highly correlated with the disease.[51,52,58,59] In the United States, national surveys indicate that the prevalence of hypertension in the population has remained relatively stable; however, the number and types of medications used to treat hypertension have increased substantially.[60] Such contrasting trends between the disease and its treatment stress the importance of investigating the role of various families of antihypertensive medications (diuretics, beta blockers, calcium channel blockers) and RCC incidence because the prevalence of hypertension has not been increasing. Moreover, the long-term effect of consuming hypertensive medications and the vascular and cellular effect on the kidney is unknown.[50,53,56]

Diabetes, also considered an emerging risk factor for RCC, may be related in part to both hypertension and obesity because obesity contributes to both conditions.[61] Results from several case-control studies have found little evidence of an association. However, before the study of diabetes as a possible risk factor can be dismissed, assessment of potential confounding by associated conditions will be required before a causal link between diabetes and RCC can be accepted.[36,61]

As stated earlier, increases in kidney cancer incidence have been reported in the United States and globally.[16,17] Attempts to explain both the increase in incidence and the racial variation by examining national and global trends of known risk factors have not been successful;[16] however, the upward trends in the prevalence of these two risk factors have varied little among race and ethnic groups.[62] Both obesity and hypertension are known risk factors for RCC and are more prevalent among blacks than whites in the United States. Recent evidence from the National Health and Nutrition Examination Survey (NHANES) suggests that age-specific increases in hypertension among black males may be playing a role.[63]

In the United States, hypertension and obesity may explain in part why RCC incidence is higher among the black population but does not account for the increases in incidence observed worldwide.[17] Smoking, an established risk factor for RCC has declined in past decades; however, the long latency of RCC could explain some but not all of the cases in older age groups. Lastly, in the United States, the largest increases in RCC have occurred for early-stage tumors. A proportional increase in early-stage tumors compared with advanced tumors could be explained by improvements in detection. However, better detection does not explain the increases observed in advanced tumors and RCC mortality.[16] This trend of rising incidence and mortality has been observed among U.S. blacks compared to U.S. whites and in several other developed countries, suggesting that risk factors are contributing to this disease.

Other risk factors that are associated with renal cancer include abuse of analgesics[4,8,57,64] and history of cystic disease due to long-term hemodialysis.[9,65,66] Excess risks have also been associated with kidney stones, cysts, and infection; however, the findings have not been consistent.[7,27,28,35,67] The role of diet has been investigated, and excess risks have been observed with consumption of certain meats and a reduced risk with certain fruits and vegetables.[29,32,68–70] Wolk et al. observed significant positive associations with total energy intake (RR 1.7; 95% CI 1.4–2.2) in the highest vs. the lowest quintile of exposure.[70] Fried meats were also associated with increased RCC risk, whereas vegetables and fruits were protective. Increased risk was also observed in those with the lowest intake (lowest decile) of vitamin E and magnesium intake. Lindbland et al. in 1997 also observed increased risk with frequent intake of fried or sautéed meat or poultry consumption, and a significantly protective effect on RCC risk was observed with increased consumption of fruit, especially citrus fruits.[71] Yuan et al. observed strong inverse trends between cruciferous and dark green vegetale intakes and RCC risk (p-trend<0.001).[72]

OCCUPATIONAL EXPOSURES

Although occupational cohort studies comprise the bulk of epidemiological literature examining employment-related kidney cancer risk, several population-based RCC case-control studies have been conducted and generally adjust occupational risk estimates for the effects of confounders such as smoking and often BMI (Table 2). Although RCC has not generally been considered an occupational cancer, several occupationally derived exposures have been implicated in a growing body of research, including asbestos, gasoline fumes, chlorinated solvents, diesel exhaust, polycyclic aromatic hydrocarbons (PAHs), printing and dyes, cadmium, and lead.

Asbestos

Asbestos fibers have been shown to induce kidney cancers in animals, and asbestos bodies can occur in kidneys of persons with asbestosis.[73–75] Several epidemiological studies have reported elevated risks among asbestos workers, shipyard

workers, insulation workers, and seafarers, as well as persons occupationally exposed to asbestos.[10,11,73,76–83] Some population-based case-control studies have found significantly elevated risks ranging from 1.4 to 1.6.[10,79] However, other population-based case-control studies and two meta-analyses of occupational cohorts with asbestos exposure have not found increased risks.[35,84–87] Positive trends with intensity[88] or duration[79–83] of exposure have not been observed. McCredie et al.[10] observed higher risks associated with the year asbestos exposure began (OR=5.28, 95% CI: 1.43–19.55; 1956–1986 vs. 1929–1948). Although elevated, exposure in this study was self-reported and may have been subject to recall bias.

Automotive Gasoline Fumes

Following a study demonstrating renal cancer among rats chronically exposed to unleaded gasoline fumes,[35,89,90] McLaughlin identified elevations in RCC risk associated with increased duration of employment among gas station attendants.[90] In addition, cohort and case-control studies among this group of workers have reported a 20–40% elevation in risk ratios, although not all findings were statistically significant.[79,90–92] Occupational gasoline exposure, both self-reported[79] and JEM-estimated,[87] has been significantly associated with RCC in two case-control studies. Other case-control studies have found no association for gasoline[7,58,93] or petroleum product exposure.[94] Partanen et al.[87] identified a dose-response relationship with respect to the estimated (ppm) and cumulative (ppm-years) exposure level (OR=4.3; 95% CI: 1.2–16.4; 14–102 ppm-years of exposure compared to controls without occupational exposure). However, an association was not observed with duration of job exposure alone. Hu et al. found a dose-response increase for self-reported (occupational and other) benzene exposure, attributing the majority of occupational benzene exposure to petroleum products.[86] Other studies found no elevation in risk.[7,81,95,96] Conflicting findings may be due to low statistical power to detect an association in the smaller case-control studies, difficulty in assessing the intensity of exposure from job title alone, geographic variation in gasoline constituents, and decrease in daily dose to gasoline attendants over time with the phase out of full-serve pumps.[97]

Solvents

Elevated rates of kidney cancer have been observed among dry cleaners, aerospace workers, aircraft maintenance workers, and architects[10,55,98–104] although not in all studies.[105–107] Schlehofer et al.[94] observed an increased risk of RCC among men reporting exposure to chlorinated solvents (OR=2.5; 95% CI: 1.2–5.2). Mandel et al.[79] reported an increase in RCC among men who reported they were ever occupationally exposed to dry cleaning solvents (OR=1.4; 95% CI: 1.1–1.7). However, when duration of occupation was considered, men in the midrange of exposure (8–25 years of exposure) had the highest level of risk.

TCE has been of particular interest due to widespread industrial use as a degreasing agent and increasing awareness of nonoccupational exposure pathways.[108] Most TCE-exposed occupational cohorts have not demonstrated statistically significant increases in risk.[103,104,106,109–112] Although not statistically significant, aerospace workers with airborne TCE exposures above 50 ppm were at a near twofold risk of kidney cancer mortality (RR=1.9; 95% CI 0.9–4.2, adjusted for age and sex), compared with workers exposed to lower levels.[103] Additional exposures to workers drinking and showering in contaminated plant well water (730–2200 ppb of TCE) were not considered.[103] Two studies have found very high risks for occupational TCE exposure,[113,114] although their validity has been questioned.[106,115] A subsequent hospital-based case-control study by the same research group found a significant association with self-reported TCE exposure and consequent narcotic symptoms.[116]

Data on TCE from population-based case-control studies are limited. Using a JEM, Pesch et al.[88] found a nonsignificant elevated risks for TCE, perchloroethylene (PCE), and all chlorinated solvents. Dosemeci et al.[117] found significantly higher (twofold) risks for renal cell cancer among women exposed to chlorinated solvents, as well as TCE, suggesting that women may be at increased risk.[117,118] Several other studies have found higher risk ratios among women compared with men, although they were not specifically designed to examine gender differences.[11,55,79,117,119,120]

Biological plausibility for the TCE/RCC link has also been derived from animal studies of TCE exposure and RCC induction, epithelial damage to the proximal renal tubules following high levels of exposure to chlorinated solvents in humans, and the more recent finding of a C to T nucleotide transition on codon 81 of the VHL gene.[121] Bruning[122] has suggested a threshold determination for TCE metabolism in humans. At low-dose exposure, the oxidative metabolic pathway is activated. At higher exposures, this pathway becomes saturated, and TCE is metabolized via glutathione conjugation, leading to the formation of damaging reactive metabolites in the proximal tubule.[122,123]

Diesel Exhaust

Occupational cohort and case-control studies have found elevated risks for RCC among truck drivers and urban bus drivers.[11,55,67,116,124,125] Brownson[67] found a significant threefold risk for heavy truck drivers (OR=3.1; 95% CI: 1.1–8.5). Using a job exposure matrix, Boffeta et al.[124] found an elevated risk for exposure to diesel exhaust in a Swedish occupational cohort, although this study did not adjust for possible confounding effects of smoking. In a population-based case-control study, Schlehofer et al. found a significantly elevated risk among men reporting occupational exhaust exposure for at least 5 years (OR=1.8; 95% CI: 1.0–3.2).[94] Constituents of diesel and motor exhausts of particular interest include polycyclic aromatic hydrocarbons (PAHs).

Polycyclic Aromatic Hydrocarbons

Elevated RCC risks among coke oven workers and petroleum refinery workers in occupational cohort studies have generated interest in PAH exposure.[79,126] Among coke oven workers, a highly increased risk, relative to other steel workers, was not replicated in the same cohort after a 30-year follow-up study.[126–128] Elevated risks in occupational cohort studies and nested case-control studies of petroleum refinery workers have not been consistent.[128–137] Other studies of occupational cohorts highly exposed to PAHs (including aluminum reduction) have found elevated but not statistically significant kidney cancer risks.[138–141] County-level kidney cancer mortality and the proportion of the population employed in petroleum refining and related industries have historically shown a crude ecologic correlation in the United States.[142] Population- and hospital-based case-control studies have found elevated risks for employment in the oil refinery industry,[55,79,90] and self-reported exposure to burning coal, petroleum, tar and/or pitch products,[35,86,95] with two of these studies providing a suggestive dose-response effect with duration of employment[35] and intensity of exposure.[95] Two population-based case-control studies that used a job exposure matrix to estimate PAH intensity found no association or dose-response effect.[87,88]

Printing and Dyes

Elevated RCC risks have been identified for printers, newspaper pressmen, paperboard printing workers, color film developers, as well as for individuals exposed to paints, pigments, and inks.[81,88,143–145] Other studies have found no association with printing industry employment.[10,11] Occupational cohorts exposed to dyes containing lead and cadmium demonstrated elevated kidney cancer mortality.[146,147] JEM-based exposure to chromium (VI) compounds, also used in inorganic dyes, leather tanning, and wood preserving, was associated with increased risk in one case-control study,[81] although concurrent exposure to lead and cadmium was not accounted for. Tanners and textile workers have shown elevated risks.[148,149] Self-reported occupational exposure to benzidine was associated with increased risk, although studies among cohorts exposed to benzidine have not clearly demonstrated an association with kidney cancer.[86]

Cadmium

Three major sources of cadmium exposure include diet, cigarette smoking, and occupation. Kolonel reported a crude association with occupational cadmium exposure.[150] Population-based case-control studies by Mandel et al.[79] and Hu et al.[86] observed a significantly elevated risk for self-reported exposure to cadmium and cadmium salts among men. Using job exposure matrices, Pesch et al.[88] observed excess risks for high exposure (OR=1.4; 95% CI: 1.1–1.8 men; OR=2.5; 95% CI: 1.2–5.3 women), and Partanen et al.[87] found elevated risk with any exposure (OR=4.4; 95% CI: 0.4–43.0), although based on only three exposed cases. Other case-control and occupational cohort studies have found no evidence of association.[10,35,151–154] Evidence of a dose-response pattern with increasing exposure intensity or duration of employment has not been found.[79,88]

Lead

Lead has been shown to induce renal cancers in animals and nephropathy among humans with high occupational exposures.[155–157] Three occupational cohort studies of lead smelter work have found a 1.4- to threefold elevation in kidney cancer mortality, depending on job area/task,[158–160] although only one demonstrated statistically significant findings.[158] Case-control studies have found significantly elevated risks among welders.[10,81,88,161–163] Welding fumes have been associated with an increased frequency of VHL gene mutations in RCC patients in a case-case comparison.[164] JEM-assessed lead exposure has been significantly associated with RCC in two case-control studies.[87,88] Studies of other lead exposed cohorts and meta-analyses of lead exposed occupational cohorts have found no statistically significant excesses of kidney cancer.[157,165,166]

Other Occupational Associations

Other industries and occupations associated with elevations in RCC risk include iron and steel industries,[87,88,163,167] metal foundries,[168] electrical utilities,[169,170] electronic equipment assembly,[88] electricians and electrical maintenance,[171] aircraft mechanics,[81,104] and firefighters.[172,173] There have been other associations reported among airline pilots,[174] farmers,[81] physicians,[166] pulp and paper mill workers,[175] railway workers,[176] miners exposed to dinitrotoluene,[177] rubber workers,[88] copper smelter work,[178] plumbers and pipefitters,[179] and metal furniture factory work.[180] Other occupational exposures investigated by a few studies include chromium (VI),[81,116] ozone,[81] jet/aviation fuel,[81,93] UV radiation,[81] styrene-butadine rubber,[81] heat stress,[139] and copper sulfate.[181]

ENVIRONMENTAL EXPOSURES

There are currently few investigations of renal cancer and carcinogenic or infectious disease agents in air, water, or food. Research to date has focused on exposures to chlorination by-products, arsenic and asbestos, in household drinking water supplies.

In an ecological study, Cantor et al. reported an increasing correlation with residual mortality (i.e., the proportion of mortality unexplained by industry, age, urban residence) as the level of trihalomethanes in drinking water of counties increased.[182] Wilkins and Comstock found no evidence of an association.[183] Yang et al. matched chlorinating and nonchlorinating communities on level of rurality and found a significantly increased risk among chlorinating communities

for both males and females.[184] In a population-based case-control study, Koivusalo et al. used historical (1950–1987) measures of turbidity and biotic components of public drinking water in an equation to estimate the level of mutagenicity in drinking water.[185] Men exposed to 3000 net revertants/litre were more likely to have developed renal cancer (OR = 1.49; 95% CI: 1.05–2.73), although a significant increase was not observed in women. Missing data for individual smoking history (43%) limited the ability of this study to adjust for possible confounding.

Several ecological studies of arsenic exposure have found elevated rates of kidney cancer in areas with high exposure to arsenic in groundwater sources.[181–190] Dose-response patterns are evident in the studies by Wu et al.[187] and Hopenhayn-Rich.[189] In a case-control study of a rural agricultural population, Kurttio et al. measured arsenic levels in drilled (not dug) wells and did not find an elevated risk of kidney cancer, although this study was limited by a small number of cases and relatively low-exposure levels.[191]

Exposure to asbestos in drinking water has been of interest due to the use of asbestos-cement pipe for transporting public water and exposure in public surface water supplies due to runoff from mine tailings. Two ecological studies of household drinking water have found significantly elevated risks for kidney cancer in men but not women[192,193] and another found only weak associations among women.[194] One study reported elevated kidney cancer mortality among women residing in counties containing an asbestos mine.[195] These studies lack information on residential history and water use patterns. A major issue has been the assumption of past exposure based on current measurements.[196] Moreover, dose-response patterns have not been investigated.

GENETIC SUSCEPTIBILITY

Numerous reports of familial RCC have thus far identified four genes that are associated with several inherited forms of kidney cancer.[197] Tumors associated with the Von Hippel Lindau (VHL) syndrome are primarily of the clear cell type and are associated with germline mutations of the *VHL* gene located on chromosome 3p.[198] VHL is a tumor suppressor gene (3p25–p26) whose protein product forms a transcription-regulatory complex targeting the α-subunits of hypoxia-inducible factor (HIF) for ubiquitin-mediated degradation in an oxygen-dependent manner.[199] Loss of VHL protein (pVHL) activity can fully activate HIF-mediated responses by stimulating the expression of hypoxia-sensitive genes involved in energy metabolism, angiogenesis, homatopoiesis, and oxygen delivery. Mutations within the β-subunit of pVHL disrupt its interaction with HIF-α subunits leading to constitutive HIF-α stabilitzation. Striking up-regulation of HIF target genes in tumors that lack functional pVHL demonstates the importance of this protein in the regulation of the HIF transcriptional cascade mediated through cellular responses to hypoxia.[199–203] Familial occurrence of RCC also has been described in the absence of the inherited VHL syndrome and has featured constitutional (3:8t) balanced translocations involving chromosome 3p.[204] In familial cases of VHL disease, patients inherit a defective tumor suppressor gene in every cell but do not develop tumors until the normal allele becomes mutated or deleted (somatic loss). In sporadic RCC, somatic VHL mutations have been observed in about 50% of tumors.[205,206] Epigenetic silencing of the gene through promoter methylation has been observed in approximately 20% of sporadic tumors.[207,208] These observations suggest that the VHL gene may be inactivated in as many as 70% of sporadic RCC tumors.

Because the VHL gene is frequently mutated in RCC, mutational spectrum analysis has been used to look for carcinogen-specific mutational fingerprints (Table 3). Bruning et al.[209] and Brauch et al.[121] provided the first possible link between trichloroethylene (TCE) and specific somatic mutations in the VHL gene in tumor DNA from highly exposed workers. A high frequency of VHL gene mutation was reported among patients with high cumulative exposure to TCE, but not among unexposed patients. More recent investigations have proposed additional hotspot mutations in this gene.[206,210] Specific types of VHL mutation have also been associated with the GSTT1 active and NAT1 slow/rapid genotypes.[205] Although the VHL mutational studies conducted to date provide promising leads for the existence of mutational hotspots among potentially susceptible populations, a larger study of the VHL mutational spectrum using improved exposure assessment methods and including information on other risk factors and confounding variables will be required to elucidate these findings.

Unlike clear cell renal carcinomas, hereditary papillary renal cancer is related to germline mutations and activation of the MET proto-oncogene located on chromosome 7p.[211] Unlike the VHL gene, MET oncogene provides the cell with positive growth signals that can lead a cell into unregulated cell cycling, morphogenesis, and eventual tumorigenesis. MET gene mutations give rise to kidney cells with mutatant hepatocyte growth factor (HGF) receptors. Unlike cells with normal receptors, these cells are unable to turn off from the activated state after HGF binding. HGF is expressed in many tissues and appears to be a cellular mitogen.[212] It is noteworthy that somatic mutations in both MET and VHL genes have been described in a high proportion of sporadic cases of papillary and clear cell cancers, respectively, implicating that alterations in these genes could play a major role in RCC development in the general population. Aside from TCE-associated VHL mutations, it is currently unknown whether specific lifestyle factors or exposures alter these genes directly.

Recent reports have identified additional genes involved in two rare inherited forms of renal cancer. The fumarate hydratase (FH) gene located on chromosome 1q42-3-q43 was recently discovered to be associated with a certain form of

TABLE 3
Mutational spectrum studies of the von Hippel-Lindau (VHL) gene and renal cell cancer (RCC)

RCC study size	Types of VHL mutations observed	Reference	Exposures
173	42% of cases mutated 4 polymorphisms identified @ nucleotide(nt) 194 (codon 65), nt 27 (codon 9), nt 183 (codon 61), nt 435 (codon 145)	[220]	Not known
227	45% of cases mutated 12% ATT.TTT at codon 147/148 Mutation prevalence was associated with stage	[210]	Not known
102	54% of cases mutated in clear cell RCC 18% of cases mutated in chromophilic tumors 6% in codon 160 5% in codon 41–45	[206]	Not known
102 (same study group as above)	Welding fumes associated with increased number of multiple mutations (OR=5.65; 95% CI: 1.39–22.93) Citrus-associated with fewer G to A transitions (OR=0.13; 95% CI: 0.03–0.57) Selenium associated with fewer G to A transitions (OR=0.31; 95% CI: 0.10–1.02) and multiple mutations (OR=0.27; 95% CI 0.07–0.97) Smoking was not a risk factor for mutations but appeared to change the outcome of many variables	[164]	Occupational exposures, lifestyle and nutritional factors while controlling for possible confounding factors
195	46% of cases mutated No hotspot observed but more tranversions occurred in cases carrying a GSTT1 active allele and in those with NAT slow/rapid genotypes	[205]	Not known
23	100% of cases mutated 30% in exon 1 44% in exon 2 26% in exon 3	[209]	Trichloroethylene
44	75% of cases mutated 52% in exon1 20% in exon 2 28% in exon 3 39% contained a hotspot mutation at nt 454 (codon 81)	[121]	Trichloroethylene

familial papillary kidney cancer.[213,214] Individuals with aberrant FH genes are also predisposed to several other dominantly inherited conditions such as uterine fibroids and skin leiomyomata. Birt-Hogg-Dubé syndrome (BHD) is another inherited form of kidney cancer that has been under study. This syndrome is primarily associated with chromophobe RCCs although clear cell tumors and hybrid chromophobe/oncocytic tumors are also commonly found.[197] The gene associated with BHD syndrome, located on chromosome 17p, is dominantly inherited.[215] Patients afflicted with BHD are also susceptible to cutaneous fibrofolliculomas and trichodiscomas on the face, neck, back, and chest; lung cysts, spontaneous pneumothorax; and multifocal or bilateral renal cancers. It is unknown whether alterations in either of these genes are observed in sporadic tumors.

Also in the genetic arena, several studies have demonstrated that individuals carrying polymorphisms in certain phase I and II metabolism genes may be at increased risk of RCC. Schultz et al. observed a 70% elevated risk of RCC in

individuals carrying the NQO1 homozygous null-allele vs. wild-type genotype.[216] Sweeney et al.[217] observed an excess of individuals carrying the inactive GSTT1 null polymorphism in cases compared with controls (OR=1.9; 95% CI: 1.1–3.4). This relationship was modified by BMI, and among those in the lowest tertile, the OR for RCC increased to 4.8 (95% CI: 1.8–13.0). Bruning et al. reported that the odds for TCE exposure in cases compared with controls were 2.7 (95% CI: 1.18–6.33) for individuals carrying the active GSTM1 polymorphism and 4.2 (95% CI: 1.16–14.91) for those carrying the active GSTT1 polymorphism.[218] Semenza et al.[219] reported that subjects carrying the slow acetylator polymorphisms of N-acetyltransferase 2 gene (NAT2) had a twofold increased risk of RCC (OR=1.8; 95% CI: 1.1–2.9). Although the OR for RCC in smokers was 2.2 (95% CI: 1.3–3.7), the risk was higher among smokers carrying the slow acetylator polymorphism (OR=3.2; 95% CI: 1.7–6.1) than among smokers carrying the rapid acetylator polymorphism (OR=1.4; 95% CI: 0.7–2.9). Longuemaux et al.[220] found the CYP1A1 variant allele to be associated with a 2.1-fold (95% CI: 1.1–3.9) increase in RCC risk. A higher risk was also observed in subjects carrying the CYP1A1 variant polymorphism when combined with the active GSTT1 polymorphism (OR=2.3; 95% CI: 1.2–4.5), the NAT2 slow acetylator polymorphism (OR=2.6; 95% CI: 1.2–5.8), and the CYP1A1 (OR=3.5; 95% CI: 1.1–11.2). Although these studies show promising hypotheses that need to be further explored, most of the studies conducted to date have been too small for analyses of gene-environment interactions (study size ranged from 50 to 220 cases). Most of these studies also lacked important information regarding other risk factors and potential confounding factors.

CONCLUSION

Results from currently available epidemiological studies provide convincing evidence linking smoking, obesity, and hypertension to an elevated risk of RCC, potentially accounting for 50% of all U.S. cases. The variation in the prevalence of these factors plus other related comorbidities, such as diabetes, across subpopulations may help to explain at least a portion of the racial and geographic variation in RCC incidence observed, not only in the United States but worldwide. The multifactorial nature of RCC requires that additional work be conducted to explain risks associated with individual factors and to elucidate complex relationships between potential genetic, lifestyle, and environmental elements on cancer development. Recently, a new unifying mechanism for the etiology of RCC has been described which unites the many risk factors associated with RCC through among different lines of research. Lipid peroxidation has been suggested as a unifying mechanistic pathway by which several risk factors, including obesity, hypertension, and chemical exposure-induced lipid peroxidation of the proximal renal tubules, could induce renal carcinogenesis.[221] This hypothesis may also explain the roles of other risk factors related to hormone status, smoking, diabetes, and protective factors such as dietary antioxidants for RCC. Although an interesting hypothesis, this possible causal mechanism has not yet been tested in vivo.

Because approximately 50% of sporatic RCC cases remain unexplained by established risk factors, more relationships need to be elucidated with respect to potential occupational and environmental exposures and cancer development. This review article covered those risk factors for which the strongest associations in humans have been noted. Epidemiological studies often have a limited ability to establish causality due to an inconsistent case definition, imprecise measures of exposure (years employed, job title, or unspecified chemical exposures), and a lack of consistent control for confounding factors (smoking, comorbidities, or other lifestyle factors). The application of biological markers of genetic susceptibility and exposure as well as intermediate biological endpoints that target RCC and conditions associated with increased risk could help to identify related factors and reduce the observed disparity in subpopulations at greatest risk. Future studies need to continue addressing these study design issues, in addition to considering underlying factors that may influence individual risk and help explain gender and racial variation of RCC.

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